NMR band IIb resulted in approximately a 10% nuclear Overhauser enhancement for the ^1H NMR band IIc_2. Since band IIb is the anomeric (C-1) proton of mycinose (2) and band IIc_2 is part of the diastereotopic methylene multiplet (C-14′) of the aglycon, the substitution pattern must be chalcose (3) at C-5 and mycinose (2) at C-14′.[9]

In summary, therefore, we have elucidated the molecular framework of a new, neutral macrolide (1) by two-dimensional NMR techniques, in conjunction with high resolution mass spectroscopic analysis.

Experimental Section

Structural assignments were derived from a variety of one-dimensional and two-dimensional (^1H NMR and ^{13}C NMR) NMR experiments carried out on a Bruker WH-250 spectrometer operating at ambient temperatures. The spectra were run in deuteriochloroform.

High resolution electron impact mass spectra were obtained on an AEI-MS 30 spectrometer. An analytically pure sample of macrolide 1 was obtained by HPLC on a Waters C-18 5 μm reverse phase column eluted with an acetonitrile–water gradient.

Anal. Calcd for $C_{35}H_{56}O_{13}$: C, 61.40; H, 8.23. Found: C, 61.27; H, 8.19.

Acknowledgment. We thank D. Sweet, R. Ware, and Dr. E. Whipple for assistance in obtaining spectra and invaluable discussions with regard to interpretations.

(8) Noggle, J.; Schirmer, R. *The Nuclear Overhauser Effect*, Academic Press: New York and London, 1971.
(9) Woo, P.; et al. *J. Am. Chem. Soc.* **1964**, *86*, 2726.

Synthesis of Vinylketenes. Thermolysis of 3-Azido-1,2-benzoquinones

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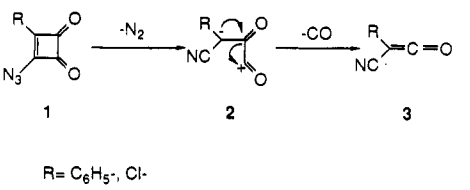
Azidocyclobutenediones 1 have previously been shown to undergo facile fragmentation to dinitrogen, carbon monoxide, and cyanoketenes 3; the zwitterionic intermediate 2 has been proposed to account for these products (Scheme I).[1-4] By analogy, it was anticipated that vinylogues of 1, i.e., 3-azido-1,2-benzoquinones 4, should cleave to the zwitterions 5 and these, in turn, suffer loss of carbon monoxide to give (2-cyanoethenyl)ketenes 6, thus providing a new entry to synthetically useful vinylketenes.[5] Reported here are the first examples of this reaction.

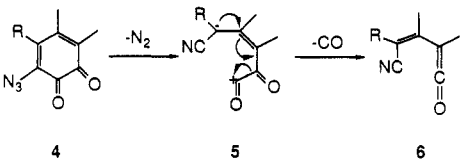
3-Azido-4,6-di-*tert*-butyl-1,2-benzoquinone (7) was subjected to thermolysis in refluxing benzene (300 mg/50 mL). Within 60 min the deep purple color of the initial solution had faded to a light yellow. The resulting residual oil was subjected to Kugelrohr distillation to give 153 mg (65%) of the ketene 9 as a light yellow oil.

The sterically hindered ketene 9 is remarkably stable. For example, at ambient temperature in methanol it requires 24 h for it to be converted to the esters 10 and 11, which are formed in 70% yield in a respective ratio of 7:3. On the other hand, the more nucleophilic cyclohexylamine reacts immediately with 9 (benzene) to give the amide 12 in 91% yield (Scheme II).

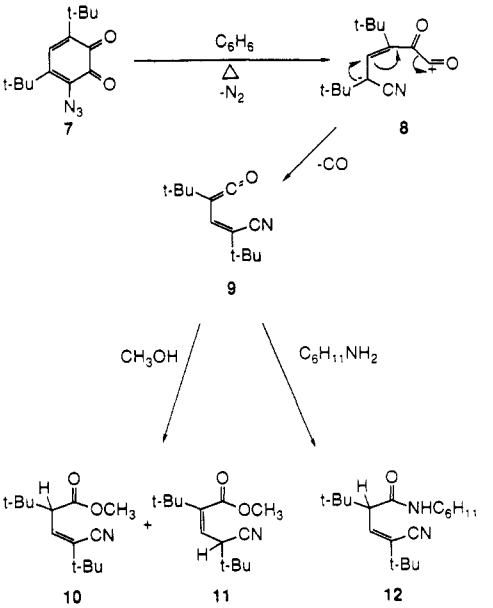
Scheme I



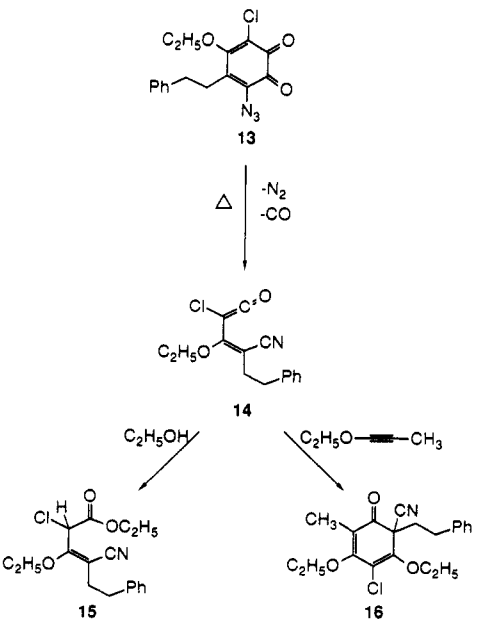
R= C_6H_5-, Cl-



Scheme II



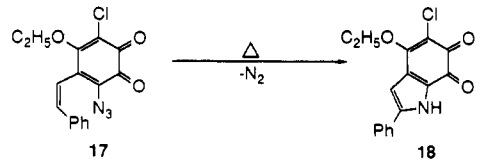
Scheme III



(1) DeSelms, R. C. *Tetrahedron Lett.* **1969**, 1179.
(2) Schmidt, H.; Ried, W. *Tetrahedron Lett.* **1969**, 2431.
(3) Fishbein, P. L.; Moore, H. W. *J. Org. Chem.* **1984**, *49*, 2190.
(4) Moore, H. W. *Acc. Chem. Res.* **1979**, *12*, 125.
(5) See, for example: Patai, S. *The Chemistry of Ketenes, Alkenes and Related Compounds*; Wiley: New York, 1980; part 1.

0022-3263/86/1951-2814$01.50/0

Scheme IV



17 18

Another example of the azidoquinone/vinylketene transformation is given in Scheme III. Here, the azidoquinone **13** was thermolyzed in refluxing benzene in the presence of ethanol or ethoxypropyne to give the ester **15** (32%) and the cyclohexadienone **16** (49%), respectively. Both are products characteristic of the intermediacy of the ketene **14**. The former is the normal ethanolysis product of the ketene. The latter constitutes a less common result but is also anticipated. It is viewed as arising from a 2 + 2 cycloaddition of the alkyne to the ketene **14**. Subsequent electrocyclic ring opening of the resulting cyclobutenone would give a dienylketene which proceeds to **16** upon cyclization. Although the regiochemistry of **16** was not rigorously established it is most likely as shown in Scheme III in accordance with the above mechanistic rational which is precedented by previous work.[6]

In an attempt to further extend the scope of this reaction, the thermolysis of the azidoquinone **17** in refluxing benzene was studied (Scheme IV). However, here a limitation to the vinylketene synthesis was observed; Rather than fragmentation to the ketene, cyclization to the red-brown indoloquinone **18** was realized (83%).[7]

Finally, the syntheses of the dichloroquinones **23** and **24** are outlined in Scheme V. These function as the precursors to the azidoquinones **13** and **17** and readily results in such upon treatment with tetramethylguanidinium azide. Alkynylation of **19** proceeds very smoothly to give the quinol **20** (84%). Reduction of the alkyne moiety in **20** can be controlled to give either **21** (90%) or **22** (84%). Hydrolysis then results in the 1,2-benzoquinones **23** (60%) or **24** (92%) respectively.

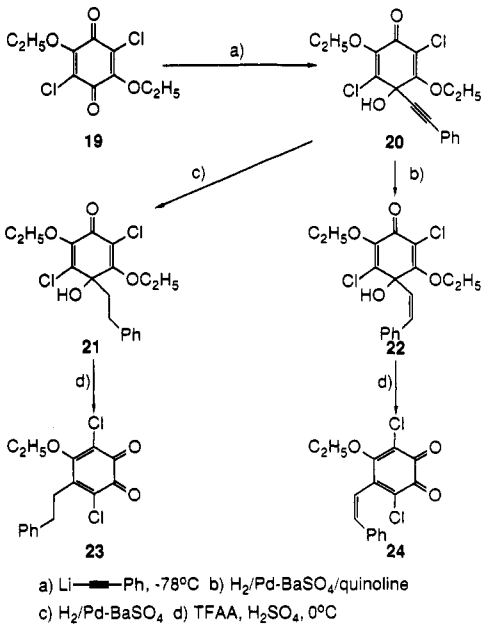
Experimental Section

3-Bromo-4,6-di-*tert*-butyl-1,2-benzoquinone. The literature procedure was slightly modified.[8] Bromine (4 mL, 78.1 mmol) in 100 mL of glacial acetic acid was added dropwise (1 h) to a solution of 3,5-di-*tert*-butylcatechol (8.0 g, 36 mmol). The light brownish yellow solution was then poured into 400 mL of water and extracted twice with 200-mL portions of methylene chloride. After the mixture was washed with water and dilute Na_2CO_3 and dried ($MgSO_4$), the solvent was removed. Recrystallization of the resulting residue from methanol gave 7.5 g (70%) of the quinone as red needles: mp 115–116 °C (lit.[8] mp 113–115 °C); IR (KBr) 3020, 2965, 1670, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (s, 1 H), 1.49 (s, 9 H), 1.25 (s, 9 H); MS (CI), *m/e* (relative intensity) 300 (14, M + 1), 302 (14), 219 (100).

3-Azido-4,6-di-*tert*-butyl-1,2-benzoquinone (7). 3-Bromo-4,6-di-*tert*-butylcatechol (200 mg, 0.67 mmol) in 50 mL of acetone was treated with tetramethylguanidinium azide (23 mL of a 0.0552 M solution, 1.34 mmol). After 20 min, 150 mL of diethyl ether was added, and the resulting mixture was washed twice with 100-mL portions of water. After drying ($MgSO_4$) and removal of the solvent, the residue was subjected to flash chromatography (SiO_2, 9:1 hexane/ethyl acetate) to afford 140 mg (80%) of a dark violet viscous oil. This was converted to the ketene without further purification. However, an analytical sample was obtained by recrystallization from hexane/ethyl acetate: mp 54–56 °C; IR (film) 2260, 2100, 1670, 1385, 1330 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 7.05 (s, 1 H), 1.34 (s, 9 H), 1.23 (s, 9 H); MS (CI), *m/e* (relative intensity) 262 (1, M + 1), 178 (100).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33. Found: C, 64.43; H, 7.54.

Scheme V



a) Li—≡—Ph, -78°C b) H_2/Pd-$BaSO_4$/quinoline
c) H_2/Pd-$BaSO_4$ d) TFAA, H_2SO_4, 0°C

(2-Cyano-3,3-dimethyl-1-butenyl)-(2,2-dimethylethyl)-ketene (9). 3-Azido-4,6-di-*tert*-butyl-1,2-benzoquinone (300 mg, 1.15 mmol) in 50 mL of anhydrous benzene was refluxed for 1 h under an atmosphere of argon. During this period the initial deep purple color faded to bright golden yellow. The solvent was removed, and the resulting oil was subjected to Kugelrohr distillation to give 153 mg (65%) of the ketene as a light yellow oil. An analytical sample was obtained by preparative GC: IR (neat) 2960, 2245, 2195, 2080 cm^{-1}; ^1H NMR δ ($CDCl_3$) 6.16 (s, 1 H), 1.20 (s, 9 H), 1.19 (s, 9 H); exact mass calcd for $C_{13}H_{19}NO$ 205.1462, found 205.1466.

Methyl 2,4-Di-*tert*-butyl-4-cyano-3-butenoate (10) and Methyl 2,4-Di-*tert*-butyl-4-cyano-2-butenoate (11). 3-Azido-4,6-di-*tert*-butyl-1,2-benzoquinone (7) (400 mg, 1.53 mmol) in 50 mL of anhydrous benzene was refluxed under argon for 75 min. Methanol (37 μL, 1.53 mmol) was then added. After 2 days, during which time the reaction was monitored by IR, the solvent was removed and the residue subjected to chromatography (SiO_2, 95:1 hexane/ethyl acetate) to give **10** (178 mg, 49%) and **11** (76 mg, 21%) as light yellow oils in an overall yield of 70%. **10** (oil); IR (neat) 2690, 2870, 2210, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.33 (d, J = 11 Hz, 1 H), 3.70 (s, 3 H), 3.41 (d, J = 11 Hz, 1 H), 1.20 (s, 9 H), 1.00 (9 H); exact mass calcd for $C_{14}H_{23}NO_2$ 222.1494, found 222.1506. **11** (oil): IR (neat) 2960, 2870, 2230, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.49 (d, J = 10.6 Hz, 1 H), 3.78 (9 s, 3 H), 3.06 (d, J = 10.6 Hz, 1 H), 1.16 (s, 9 H), 1.04 (s, 9 H); exact mass calcd for $C_{14}H_{23}NO_2$ 222.1494, found 222.1498.

***N*-Cyclohexyl-2,4-di-*tert*-butyl-3-butenamide (12).** The ketene **9** was generated as described above from 360 mg (1.38 mmol) of the azidoquinone **7**. Cyclohexylamine (160 μL, 1.38 mmol) was then added and the reaction solution stirred for 12 h. After removal of the solvent the residue was purified by flash chromatography (SiO_2, 9:1 hexane/ethyl acetate) to give 380 mg (91%) of **12** as white needles: mp 150–151 °C; IR (KBr) 3320, 2905, 2235, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.56 (d, J = 12.1 Hz, 1 H), 3.80 (br s, 1 H), 3.03 (d, J = 12.1 Hz, 1 H), 1.50 (m, 1 H), 1.18 (s, 9 H), 1.05 (s, 9 H); MS (CI, M + 1), *m/z* (relative intensity) 305 (100).

Anal. Calcd for $C_{18}H_{31}NO_2$: C, 75.20; H, 10.30. Found: C, 74.99; H, 10.26.

Ethyl 2-Chloro-4-cyano-3-ethoxy-4-phenethyl-3-butenoate (15). A solution of 3-azido-6-chloro-5-ethoxy-4-phenethyl-1,2-

(6) For close analogies, see: Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. Fishbein, P. D.; Moore, H. W. *Ibid.* **1985**, *50*, 3226.

(7) It has previously been shown that 2-azido-3-alkenyl-1,4-benzoquinones give indoloquinones upon thermolysis. See: Germeraad, P.; Moore, H. W. *J. Org. Chem.* **1974**, *39*, 774.

(8) Heis, J.; Zeller, K.-P.; Riecker, A. *Org. Mass Spectrom.* **1969**, *2*, 1325.

benzoquinone (13) (250 mg, 0.75 mmol) in absolute ethanol was refluxed for 2 h. The solvent was then removed, and the dark brown residue was subjected to flash chromatography (SiO_2, 9:1 hexane–ethyl acetate) to give 15 as a light yellow oil (77 mg, 32%): IR ($CHCl_3$) 2210, 1735, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.34 (m, 5 H) 4.55–4.66 (m, 2 H), 4.22–4.38 (m, 2 H), 3.88–4.00 (m, 5 H) 3.70–3.82 (m, 1 H), 2.79–2.89 (m, 2 H), 1.30 (t, J = 7 Hz, 2 H), 1.20 (t, J = 7 Hz, 2 H); exact mass calcd for $C_{17}H_{20}ClNO_3$ 321.1130, found 321.1140.

4-Chloro-6-cyano-3,5-diethoxy-2-methyl-6-phenethyl-2,4-cyclohexadienone (16). A solution of the azide 13 (300 mg, 0.90 mmol) and ethyl propynyl ether (4 mL, 40 mmol) in 50 mL of anhydrous benzene was refluxed for 2 h. After removal of the solvent the residue was subjected to flash chromatography (SiO_2, 8:2 hexane/ethyl acetate to give 159 mg (49%) of 16 as a bright yellow oil: IR ($CHCl_3$) 2240, 1665, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H), 4.50–4.61 (m, 1 H), 4.28–4.40 (m, 1 H), 4.00–4.15 (m, 2 H), 2.40–2.68 (9 m, 4 H), 1.88 (s, 3 H), 1.46 (t, J = 7 Hz, 2 H), 1.45 (t, J = 7 Hz, 2 H); exact mass calcd for $C_{20}H_{22}ClNO_3$ 359.1288, found 359.1269.

5-Chloro-4-ethoxy-2-phenyl-6,7-indoloquinone (18). A solution containing 100 mg of the azidoquinone 17 (0.30 mmol) in 10 mL of benzene was refluxed for 6 h. As the reaction progressed 18 precipitated from the reaction solution. The reaction mixture was cooled and filtered and the filtrate washed with diethyl ether to give 62 mg (68%) of 18 as fine deep red crystals: mp >200 °C dec; IR (KBr) 3330, 1680, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.03 (m, 1 H), 7.53 (m, 5 H), 7.23 (s, 1 H), 2.24 (s, 3 H); exact mass calcd for $C_{15}H_{10}ClNO_2$ 271.0400, found 272.0395.

2,5-Dichloro-3,6-diethoxy-4-hydroxy-4-(2-phenylethynyl)-2,5-cyclohexadienone 20. Phenylacetylene (20.5 mL, 187 mmol) was dissolved in 300 mL of anhydrous THF and cooled to −78 °C under argon. Butyllithium (16.3 mL, 10.5 M solution, 171 mmol) was added over a 5-min period. The acetylide salt mixture was then allowed to stir for 1 h at −78 °C. The mixture was transferred dropwise via cannula to a stirred suspension of 2,5-dichloro-3,6-diethoxy-1,4-benzoquinone (41.2 g, 156 mmol) in 1300 mL of anhydrous THF at −78 °C. The addition took place over a 1-h period, during which the color of the solution turned dark brown. After an additional 2.5 h the reaction was quenched by the addition of 1.1 equiv of glacial acetic acid (9.8 mL). The solution was then concentrated and the residue dissolved in 800 mL of diethyl ether. This was washed twice with 200-,L portioins of water and the dried over $MgSO_4$. After removal of the solvent the resulting dark brown residue was recrystallized from diethyl ether/hexane to give 48 g (84%) of 20 as yellow crystals: mp 104–106 °C; IR ($CHCl_3$) 3400, 3050, 2980, 2935, 2100, 1665, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.48 (m, 5 H), 4.72–4.84 (m, 2 H), 4.13–4.19 (m, 2 H), 3.76 (s, 1 H), 1.49 (t, J = 7 Hz, 3 H), 1.37 (t, J = 7 Hz, 3 H).

2,5-Dichloro-3,6-diethoxy-4-hydroxy-4-phenethyl-2,5-cyclohexadienone (21). A suspension of 200 mg of 5% Pd–$BaSO_4$ and 1 g of 20 in 150 mL of ethyl acetate was subjected to a slight positive pressure of hydrogen for 30 min. Filtration and removal of the solvent gave a pale yellow solid, which was recrystallized (diethyl ether/petroleum ether) to yield 91 mg (90%) of 21 as white crystals: mp 78–79 °C; IR (KBr) 3420, 3020, 2950, 2930, 1645, 1590, 1200, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06–7.23 (m, 5 H), 4.49–4.69 (m, 2 H), 4.01–4.20 (m, 2 H), 3.09 (s, 1 H), 2.20–2.50 (m, 4 H), 1.44 (t, J = 7 Hz, 3 H), 1.37 (t, J = 7 Hz, 3 H); MS (CI), m/e (relative intensity) 371 (100, m + 1).

Anal. Calcd for $C_{18}H_{20}ClO_4$: C, 58.23; H, 5.43. Found: C, 58.07; H, 5,63.

2,5-Dichloro-3,6-diethoxy-4-hydroxy-4-[(*Z*)-2-phenylethenyl)-2,5-cyclohexadienone 22. A suspension containing 1 g of 20, 100 mg of quinoline, and 200 mg of 5% Pd–$BaSO_4$ in 150 mL of ethyl acetate was subjected to a slight positive pressure of hydrogen for 90 min. The product was then isolated and purified as described above to yield 84 mg (84%) of 22 as white crystals: mp 131–132 °C; IR (KBr) 3400, 3080, 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.25 (m, 3 H), 7.00–7.10 (m, 2 H), 6.79 (d, J = 11.5 Hz, 1 H), 5.80 (d, J = 11.5 Hz, 1 H), 4.40–4.65 (m, 2 H), 3.60–3.80 (m, 2 H), 3.52 (s, 1 H), 1.43 (tJ = 7 Hz, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS (CI), m/e (relative intensity) 369 (15, M + 1), 323 (100).

Anal. Calcd for $C_{18}H_{18}Cl_2O_4$: C, 58,55; H, 4.91. Found: C, 58.69; H, 4.87.

3,6-Dichloro-4-ethoxy-5-phenethyl-1,2-benzoquinone (23). To a solution of 21 (2.29 mmol) in 50 mL of dry diethyl ether was added 0.65 mL of trifluoroacetic anhydride. The solution was refluxed for 1 h and then allowed to cool to room temperature. Concentration H_2SO_4 (5 drops) was then added and the solutioin immediately became bright red in color. After 5 min 200 mL of petroleum ether was added and the solution immediately cooled in a dry ice/acetone bath. The resulting precipitate was obtained by filtration to give 450 mg (60%) of 21 as bright red crystals: mp 148.5–150 °C; IR (KBr) 3040, 2980, 1670, 1605, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.72 (q, J = 7 Hz, 2 H), 3.01 (m, 2 H), 2.85 (m, 2 H), 1.51 (t, J = 7 Hz, 3 H); MS (CI), m/e (relative intensity) 327 (18, M + 2), 71 (100).

Anal. Calcd for $C_{16}H_{14}Cl_2O_3$: C, 59.10; H, 3.10. Found: C, 59.01; H, 3.06.

3,6-Dichloro-4-ethoxy-5-[(*Z*)-2-phenylethenyl]-1,2-benzoquinone (24). By the procedure described above 1 g (2.71 mmol) of 22 was converted to 0.81 g (92%) of the red crystalline quinone 24: mp 90–92 °C; IR (KBr) 2950, 1670, 1605, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.36 (m, 5 H), 6.97 (d, J = 11 Hz, 1 H), 6.48 (d, J = 11 Hz, 1 H), 4.38 (q, J = 7 Hz, 2 H), 1.18 (t, J = 7 Hz, 3 H); MS (CI), m/e (relative intensity) 325 (100, M + 1).

Anal. Calcd for $C_{16}H_{12}Cl_2O_3$: C, 59.46; H, 3.74. Found: C, 59.41; H, 3.83.

3-Azido-6-chloro-5-ethoxy-4-phenethyl-1,2-benzoquinone (13). A solution containing 244 mg (0.75 mmol) of the quinone 21 in 50 mL of diethyl ether was cooled to 0 °C and then 5.4 mL (0.75 mmol) of a 0.139 M solution of tetramethylguanidinium azide solution (acetone) was added over a 3-min period. During the addition the color of the solution became a deep purple. After 5 min the reaction solution was washed twice with water and dried ($MgSO_4$) and the solvent then removed to give a deep purple crystalline solid (220 mg, 88%): mp 108–109 °C; IR ($CHCl_3$) 2005, 1670, 1605, 1535; ^1H NMR ($CDCl_3$) δ 7.29 (m, 5 H), 4.69 (q, J = 7 Hz, 2 H), 2.78 (s, 4 H), 1.49 (t, J = 7 Hz, 3 H); exact mass calcd for $C_{16}H_{14}ClN_3O_3$ 331.0721, found 331.0738.

3-Azido-6-chloro-5-ethoxy-4-[(*Z*)-2-phenylethenyl]-1,2-benzoquinone (17). By a procedure analogous to the above, 22 (120 mg, 0.37 mmol) was converted to the titled azidoquinone as a dark greenish red solid (62 mg, 68%): mp >200°C dec; IR (KBr) 3230, 1635, 1460, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.89 (d, J = 11 Hz, 1 H), 6.14 (d, J = 11 Hz, 1 H), 4.42 (q, J = 7 Hz, 2 H), 1.22 (t, J = 7 Hz, 3 H).

Acknowledgment. We thank the National Institutes of Health (CA-11890, AI-15651) and the National Science Foundation (CHE-25567) for financial support of this work.

Registry No. 6, 102343-62-4; 7, 102343-59-9; 7 (3-bromo), 27807-90-5; 9, 102343-60-2; 10, 102343-61-3; 12, 102367-87-3; 13, 108-91-8; 15, 102343-63-5; 16, 102343-64-6; 17, 102343-65-7; 18, 102343-66-8; 20, 102343-67-9; 21, 102343-68-0; 22, 102343-69-1; 23, 102343-70-4; 24, 102343-71-5; $C_2H_5OC{\equiv}CCH_3$, 14273-06-4; $PhC{\equiv}CH$, 536-74-3; 3,5-di-*tert*-butylcatechol, 1020-31-1; 2,5-dichloro-3,6-diethoxy-1,4-benzoquinone, 20764-96-9; 3-azido-6-chloro-5-ethoxy-4-phenethyl-1,2-benzoquinone, 102343-72-6; 3-azido-6-chloro-5-ethoxy-4-[(*Z*)-2-phenylethenyl]-1,2-benzoquinone, 102343-73-7.